

## REMARKS

### Summary of the Invention

The invention features methods for assaying a compound for its ability to affect cell division, by determining whether the compound affects the interaction between an isolated ER $\beta$  polypeptide or an ER $\beta$  polypeptide fused to glutathione-S-transferase, and mitosis arrest deficient 2 (MAD2).

### Support for the Amendment

Support for the amendment to the specification is found in Fig. 3A and throughout the specification. Applicant submits that one skilled in the art would recognize that the term “amino acids” was mistakenly used in the place of “nucleotides” in the specification as filed and, based on the context, would understand that these passages were meant to refer instead to the nucleic acid sequence of mouse ER $\beta$ . The mouse ER $\beta$  gene sequence is 1458 nucleotides long (see, e.g., GENBANK accession number AJ000220; provided herewith). This translates into a polypeptide having 485 amino acids, which clearly does not contain amino acids 516 to 641, to which the passage refers. The nucleotide sequence does, however, contain nucleotides 516 to 641. Furthermore, the specification clearly refers to restriction enzyme digestion (see, e.g., page 16, lines 3-4), which occurs with nucleic acid molecules, not amino acids. Accordingly, amendment of the specification to substitute “nucleotides” in place of “amino acids” should be permitted.

Support for the amendment to claim 1 is found on page 7, line 13, through page 8, line 5, page 16, lines 19-20, and claim 1 as originally filed. Although the term “isolated” is not present in the specification, *ipsis verbis* disclosure is not necessary to satisfy the written description requirement of 35 U.S.C. § 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question. Here, the specification at page 7, line 2, through page 8, line 5, clearly indicates that the ER $\beta$  that is employed in the recited assays is isolated, i.e., not in its naturally occurring state mixed together with numerous other substances with which it naturally occurs. (*In re Edwards*, 568 F.2d 1349, 1351-52, 196 U.S.P.Q. (BNA) 465, 467 (CCPA 1978).) Support for the amendment to claim 2 is found on page 4, line 13, and Figure 2B. Support for the amendment to claim 6 and for new claim 9 is found on page 17, lines 7-17, and Fig. 3A.

Applicant has also added new claim 10, which recites SEQ ID NO: 7. Applicant provides herewith a new sequence listing containing three additional sequences. SEQ ID NO: 5 is the nucleotide sequence of mouse ER $\beta$ . SEQ ID NO: 6 is the amino acid sequence of mouse ER $\beta$ . SEQ ID NO: 7 is the amino acid sequence encoded by nucleotides 516 to 641 of mouse ER $\beta$ . The sequence of mouse ER $\beta$  was known in the art prior to Applicant’s filing date (see, e.g., GENBANK accession number AJ000220, submitted July 15, 1997; Tremblay et al., *Molecular Endocrinology* 11:353-365, 1997; and Pettersson et al., *Molecular Endocrinology* 11:1486-1496, 1997; a copy of each

reference is provided herewith). Support for SEQ ID NO: 7 is found on page 16, line 18, through page 17, line 1, and Fig. 3A.

No new matter is added by the amendment.

#### The Office Action

Claims 1-3 and 6 are pending. Claims 1-2 are rejected under 35 U.S.C. § 101 for being directed to non-statutory subject matter. Claims 1-3 and 6 are rejected under 35 U.S.C. § 112, first and second paragraph, for lack of written description and indefiniteness, respectively. Claims 1 and 3 are rejected under 35 U.S.C. § 102(b) for anticipation by Iafrati et al. (Nature Medicine 3:545-548, 1997; hereinafter “Iafrati”).

#### Rejections under 35 U.S.C. § 101

Claims 1 and 2 are rejected under 35 U.S.C. § 101 for being directed to non-statutory subject matter. The Examiner rejects claims 1 and 2 based on the premise that the subject matter, as originally claimed, “reads upon a process which occurs in nature and which does not show the hand of man.” As was suggested by the Examiner, Applicant has amended claim 1 to recite “isolated estrogen receptor beta (ER $\beta$ ) and mitosis arrest deficient 2 (MAD2).” (Emphasis added.) Accordingly, Applicant requests that the rejection of claims 1 and 2 under 35 U.S.C. § 101 be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-3 and 6 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Claim 1 is rejected for reciting “potentially capable of affecting cell division.” Claim 1 now recites that a test compound is capable of affecting cell division if it affects ER $\beta$ /MAD2 complex or complex formation. In addition, claim 1 now defines the acronyms “ER beta,” as “estrogen receptor beta (ER $\beta$ ),” and “MAD2” as “mitosis arrest deficient 2 (MAD2).” Applicant notes that the term “EC1” is not an acronym, but instead refers to a specific MAD2 clone identified from an ovine library, and which is defined in the specification on page 14, line 11, through page 15, line 5.

The Examiner also rejects claim 2 for reciting “‘MAD2 is clone EC1’ which is ambiguous...” Applicant has amended claim 2 to recite “said MAD2 is encoded by a nucleic acid molecule comprising the sequence set forth in SEQ ID NO: 3,” which corresponds to the nucleic acid sequence that encodes EC1. Accordingly, Applicant requests that the rejection of claim 2 be withdrawn.

The Examiner rejects claim 6 for being confusing and ambiguous with regard to the role of the GST-fusion protein in the determination step. Claim 6, as amended, now recites that ER $\beta$  additionally comprises glutathione-S-transferase and the determination of whether a test compound affects GST-ER $\beta$ /MAD2 complex or complex formation is made using a GST-fusion protein interaction assay, which is described in the specification on page 17, line 7, through page 20, line 18. Therefore, Applicant requests that the

rejection of claim 6 be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-3 and 6 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner states:

[The] terms “ER beta,” “MAD2,” and “MAD2 is clone EC1”...[encompass]...variant protein because no structural limitation is provided...[and] the disclosure does not have written description for the genus of variants. One skilled in the art cannot envision the sequence of all the variants of proteins encompassed by the claim limitation.

Applicant respectfully traverses the rejection.

A patent specification does not need to describe exactly all the subject matter that is claimed. (*In re Daniels*, 114 F.3d 1452, 46 U.S.P.Q.2d 1788 (Fed. Cir. 1998); *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 227 U.S.P.Q. 117 (Fed. Cir. 1985).) Rather, Applicant needs only communicate to those skilled in the art that the claimed subject matter is intended to be part of their invention. As was stated by the Federal Circuit in *Martin v. Mayer*, 823 F.2d 500, 3 U.S.P.Q.2d 1333 (Fed. Cir. 1987):

[T]he specification must ‘convey clearly to those skilled in the art to whom it is addressed...the information that [the inventor] has invented the specific subject matter later claimed.’

Moreover, the M.P.E.P. § 2163.02 (Eighth Edition, August 2001) states:

[A]n objective standard for determining compliance with the written description requirement is, “does the description

clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (emphasis added).”

In applying this standard, the Federal Circuit has held that the specification must convey with reasonable clarity to a skilled artisan that the inventor “was in possession of the invention” at the time of filing. (*Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991).) Moreover, in *Regents of the University of California v. Eli Lilly and Co.* (119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997)), the Federal Circuit acknowledged that “every species in a genus need not be described in order that a genus meets the written description requirement.” (43 U.S.P.Q.2d at 1405 (citing *Utter v. Hiraga*, 845 F.2d 993, 6 U.S.P.Q.2d 1709 (Fed. Cir. 1988) (“A specification may, within the meaning of § 112, ¶ 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.”))) The *Lilly* court further acknowledged that “it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified ... by other appropriate language.” (*Lilly*, 119 F.3d at 1569.)

Applicant has plainly met these standards. The written description requirement is satisfied by the description of ER beta and MAD2 found within the specification because the functional properties of these polypeptides are clearly described in the specification. For example, the ability of ERβ to act as a transcription factor upon binding estrogen is described on page 1, lines 9-10, and the estrogen-dependent vascular protective effect of ERβ is described in Iafrati et al., *Nature Medicine* 3:545-548, 1997, which is incorporated into the specification by reference (see page 1, line 16, through page 2, line 3, of the

specification). MAD2, which functions as a cell cycle checkpoint protein, is described in the specification on page 5, line 6, through page 6, line 7, and in Elledge, Science 279:999-1000, 1998, also incorporated into the specification by reference. In addition, a structural description of one representative species of ER $\beta$  (mouse ER $\beta$ ) and two representative species of MAD2 (human MAD2 and sheep MAD2 (i.e., EC1) is provided in Fig. 3A and Figs. 2A and 2B, respectively. These representative species share greater than 80%, and in most cases greater than 90%, sequence identity with other known ER beta and MAD2 homologs.

Given this level of sequence identity, the description provided in the present specification clearly indicates to one skilled in the art that Applicant was in possession of the invention, as is now claimed, at the time of filing, which is the standard for determining compliance with the written description requirement as described in *In re Gosteli* (872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)) and *Vas-Cath, Inc. v. Mahurkar* (supra).

Finally, Applicant notes that the presently claimed invention provides a method of determining an interaction between ER $\beta$  and MAD2, irrespective of the particular species. Because the level of sequence identity between the various species within the genus of ER $\beta$  and MAD2 is high, Applicant submits that the method will work regardless of the species of ER $\beta$  or MAD2 used. Therefore, based on the foregoing remarks,

Applicant respectfully requests that the rejection of claims 1-3 and 6 under 35 U.S.C. § 112, first paragraph, be withdrawn.

#### Rejections under 35 U.S.C. § 102

Claims 1 and 3 are rejected under 35 U.S.C. § 102(b) for anticipation by Iafrati. The Examiner states that “Iafrati et al. teach the method of determining vascular cell proliferation when [vascular cells, which express estrogen receptor beta, are] treated with estradiol...The vascular cells inherently express...MAD2.” Applicant respectfully disagrees.

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” (*Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051,1053 (Fed. Cir. 1987).) The Examiner asserts that Iafrati discloses all of the elements of present claims 1 and 3 by relying on the inherency of MAD2 expression in vascular cells. But even if MAD2 is expressed by vascular cells, Iafrati does not anticipate present claims 1 and 3 because Iafrati fails to disclose an interaction between ER $\beta$  and any other protein, let alone MAD2, and therefore did not suggest adding a test compound to determine whether it would affect the interaction. Therefore, there is no inherent disclosure of the claimed invention in the reference. Further, the Federal Circuit has held that a “retrospective view of inherency is not a substitute for some teaching or



suggestion which supports the selection and use of the various elements in the particular claimed combination.” (*In re Newell*, 891 F.2d 899, 13 USPQ2d 1248 (Fed. Cir. 1989), cert. denied, 493 U.S. 814 (1989).) Furthermore, “The mere fact that a certain thing may result from a given set of circumstances is insufficient to prove anticipation.” (*Electro Medical Systems, S.A. v. Cooper Life Science, Inc.*, 34 F.3d 1048, 32 USPQ2d 1017 (Fed. Cir. 1994).)

“‘Inherency’ charges the inventor with knowledge that would be known to the art, although not described. Inherency is not a matter of hindsight based on applicant’s disclosure: the missing claim elements must necessarily be present in the prior art.” (*In re Schreiber*, 128 F.3d 1473, 44 USPQ 1429 (Fed. Cir. 1997).) Finally,

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.” (*Continental Can Company USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 20 USPQ2d 1746 (Fed. Cir. 1991).)

The Examiner’s retrospective view of inherency of the claimed invention based on Applicant’s specification is not a substitute for a teaching supporting an anticipation rejection and, as is indicated above, this is not an appropriate basis for a rejection under 35 U.S.C. § 102. The Examiner must provide some evidence in the prior art that describes the missing elements of claims 1 and 3 (i.e., an interaction between ER $\beta$  and MAD2, and use of a test compound to test its ability to affect that particular interaction).

Based on the foregoing remarks, Applicants request that the rejection of claims 1 and 3 under 35 U.S.C. § 102 be withdrawn.

CONCLUSION

Applicant submits that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a petition to extend the period for replying for three months, to and including September 26, 2002. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Version with markings to show changes made

In the specification:

A marked-up version of the specification on page 16, line 17, through page 17, line 4, is presented below.

--Assay of the truncation mutants proved to be a sensitive and specific screen for the identification of the MAD2/ER beta interaction domain. The interaction domain was identified as encompassing nucleotides [amino acids] 516 to 622 of ER beta (Fig. 3A). Fig. 3B summarizes the two hybrid protein interaction results. As is shown in Fig. 3B, the ER beta/MAD2 interaction domain is defined by nucleotides [amino acids] 516 to 641 of ER beta that interact with MAD2 clone EC1. Fig. 3B also shows that slightly larger regions containing the interaction domain support the interaction between ER beta and MAD2, while fragments lacking nucleotides [the] 516-622 of ER beta [amino acid domain] do not.--

A marked-up version of the specification on page 20, lines 3-15, is presented below.

--Thus the GST-fusion protein experiments demonstrate that mER $\beta$  is brought down, or associates with, the GST-MAD2 clone and, in the converse experiment, MAD2 is brought down by GST-mER $\beta$ . Each case demonstrates the protein-protein interaction. In contrast, the results shown in Fig. 4C indicate that while GST-mER $\beta$ , as expected, brings down ER $\alpha$  [alpha] (this is a positive control since it is known that these two proteins heterodimerize), GST alone, or GST MAD2, shown in the third and fourth lanes, respectively, do not bring down ER $\alpha$  [alpha]. This result confirms the two hybrid data, i.e. that ER $\alpha$  [alpha] does not interact with MAD2. Fig. 4D, which shows the results of protein- protein interaction studies between MAD2 and ER beta mutants, also confirms the two hybrid data which identified the MAD2/ER beta interaction domain as including nucleotides [amino acids] 516-622 of ER beta. Other experiments indicate that MAD2 does not interact with RAR or RXR (two steroid hormone families members), further underscoring the specificity of the MAD2/ER beta interaction.--

In the claims:

A marked-up version of claims 1, 2, and 6 is presented below.

1. (Amended) A method for determining whether a test compound is [potentially] capable of affecting cell division, said method comprising:

a) contacting said test compound with isolated estrogen receptor beta (ER $\beta$ ) [ER beta] and mitosis arrest deficient 2 (MAD2), or a binding fragment [or binding fragments] thereof, under conditions in which ER $\beta$  [ER beta] and MAD2, or a fragment thereof, [or fragments] have formed, or are able to form, a complex[,] ; and

b) determining whether said test compound affects said ER $\beta$  [ER beta]/MAD2 complex or complex formation, as an indication that said test compound is [potentially] capable of affecting cell division.

2. (Amended) The method of claim 1, wherein said MAD2 is encoded by a nucleic acid molecule comprising the sequence set forth in SEQ ID NO: 3 [clone EC1].

6. (Amended) The method of claim 1, wherein said ER $\beta$  additionally comprises glutathione-S-transferase (GST) and said complex or complex formation is determined using a [determining is done by] GST-fusion protein interaction assay.